A Brief Journey of Tocotrienols as Anticancer Agents

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Abstract

The journey of tocotrienol is started when the Vitamin E was first discovered as the fertility factor. Later in the research studies vitamin E was found to be consisting of eight isomers which can be divided into two separate groups known as tocopherols and tocotrienols. The isomers share similarity in structure but differ at much levels based upon their functional or biological properties. Initially tocopherols were investigated much due to their powerful antioxidant properties. However, the other four isomers of tocotrienols were found to be consisting of anticancer properties at varying degree in vitro and in vivo. The mechanisms mediated by tocotrienols such as NFKB pathway, apoptosis, and effect on DNA polymerases are totally different to those of tocopherols.

Keywords: Tocotrienols; Vitamin E; Anticancer activity; Tocopherols

Introduction

Natural compounds have been studied in various fields since many decades for their pharmacological activities [1-3]. When the Vitamin E was first identified, the α-tocopherol was found to be possessing potent antioxidant property [4]. Later four isomers of tocopherols known as α, β, γ, and δ tocopherols were identified which differ from each other based upon the methyl group substitution on the chromanol ring which also have varying potency of antioxidant property. Other four isomers of vitamin E were identified later which differ from their respective tocopherols based upon the unsaturation of the isoprenoid side chain (Figures 1-2) [5]. Tocotrienols became main interest research after they were proven to be effective anticancer agents [6]. Palm oil, rice bran oil, grape fruit seed oil, oats, hazelnuts, maize, olive oil, Buckthorn berry, rye, flax seed oil, poppy seed oil and sunflower oil are natural sources of tocotrienols at varying yields [7].

Tocotrienols have the unsaturated side chain which is useful for their penetration into the various organs and fatty tissues [8]. Structurally tocotrienols contain three major parts. The phenolic hydroxyl group is essential for their antioxidant activity. Phytyl side chain is essential for their membrane binding and further absorption. However, the oral absorption of tocotrienols is very negligible when compared to the tocopherols due to their lower association with α-tocopherol transfer protein (α-TTP) [9]. However, tocotrienols need to be absorbed in the similar fashion to tocopherols. Presence of food increases their absorption. Tocotrienols form micelles in the gut and form chylomicrons which can be further entered into the lymphatic system.

The rate limiting step for bioavailability of any compound is their absorption and metabolism [10]. Tocopherols and tocotrienols are degraded by same mechanism because of their structural similarity. First, cytochrome p450 enzymes carry the ω hydroxylation on the tocols [11]. Most probable CYP enzymes in this are cyp3A4 and cyp4F2. Next, β oxidation takes place. The final products of all forms are the respective carboxyethylhydroxychromans (CEHC). These chromans are more aqueous soluble and excreted in urine [11].

Figure 1: Structure of tocotrienols.
Anticancer Activities of Tocotrienols

Cancer is the biggest threat to mankind due to its aggressive, uncontrollable growth and metastatic properties [22-26]. The first ever anticancer activity of tocotrienols was found by Komiyama et al. The research group developed tumor model in mice by injecting cells i.p. and further treated them with tocopherol or tocotrienols i.p. injections. The results indicated that γ tocotrienol increased life expectancy in mice with fibrosarcoma compared to the α tocotrienol and tocopherols but does not have any significant anticancer activity against P388 leukemia [27]. The study also further had insights on tocotrienol mediated anticancer activity towards human and mouse cell lines in vitro. Further the agents do not have significant toxicity on the animals [27].

Later many other research groups extended their study on the anticancer properties of the tocotrienols against various cancer types. When chemically induced tumor bearing rats were given a diet of corn oil, palm oil and soya bean oil, it was observed that palm oil fed rats have lower incidence of tumor appearance and also lower number of tumors compared to the other two groups [28]. In different set of studies, it was observed that the palm oil is the major source of Tocotrienols which are proven to be the potent in vitro anticancer agents [29-31]. Palm oil represents one of the most abundant natural sources of tocotrienols [31].

In similar experiments in rats, tocotrienol activity was measured in hepato-carcinogenesis. Rats were fed with 2-acetylaminoflourene (AAF) and treated with tocotrienols for few weeks [32]. Results indicated that the tocotrienol treated rats have lower tendency to show liver cell damage compared to the AAF alone treated mice. The effects of tocotrienol were measured by the decreased activities of both plasma and liver microsomal gamma-glutamyl transpeptidase (GGT) and liver microsomal UDP-glucuronyl transferase (UDP-GT). This strongly suggests the tocotrienol reducing effect on severity of hepato carcinogenesis [32].

Among all the cancers, breast cancer is the mostly studied to evaluate the anticancer activity of tocotrienols [13,33-35]. In one of the studies, tocotrienols displayed potent in vitro anticancer activity against highly malignant +SA mammary cancer cells with minimum toxicity on the normal mammary epithelial cells. At the same time, even higher doses of tocopherols did not have any significant anticancer activity on the same malignant cells [36]. The anticancer activity was measured in the terms of decreased proliferation. Further it was shown that tocotrienol mediated decreased mammary cancer cell proliferation was mediated by decreased Akt activity and NFκB transcriptional down regulation [37].

Even significant research was done to show the apoptotic ad other pathway mediated anti proliferative activity of tocotrienols, it is not clear at the gene level. In one study oestrogen dependent and independent mouse mammary cancer cells were treated with tocotrienols and further DNA micro array was performed [38]. The results indicated three affected gene regulators including c-myc binding protein MM-1, 23-kDa highly basic protein, and interferon-inducible...
protein 9-27 (IFITM-1). These are essential in cell cycle progression, and differentiation of tumor cells [38].

Annatto seeds being the major source of tocotrienols, Annatto T3 was investigated for its in vitro and in vivo anticancer activity in HER-2/new transgenic mice [39]. The experimental mice were studies for apoptosis, senescent like growth arrest, immune modulation and oxidative effect. Results indicated strong anticancer activity of annatto tocotrienol in terms of reduced number of tumors, decreased tumor size and lung metastatic tumors. However, no significant immune modulation was observed. This is the first ever spontaneous breast cancer model in mice with annatto tocotrienol supplementation [39].

Other studies showed that dietary supplementation with TRF inhibited growth of 4SA mammary tumors transplanted in female syngeneic BALB/c mice [40]. However, these antitumor effects of dietary TRF supplementation did not produce a typical dose-responsive effect. These findings indicate that the anticancer effectiveness of oral administration of tocotrienols may be limited due to inefficient or saturated uptake/transport mechanisms within the gut and circulation. Nevertheless, experimental evidence strongly suggested that tocotrienols provide potential health benefits in the treatment of cancer [40].

Targeted Delivery of Tocotrienols

Maintaining desired concentrations of tocotrienols at target is difficult to achieve because of their low bioavailability and increase excretion rate. Few studies were conducted to improve their in vivo activity by making semi synthetic derivatives which had shown promising results in mice model of breast cancer [41-43]. In a recent published article, tocotrienol was targeted by using targeted vesicles [44]. These vesicles were conjugated by transferrin and loaded with either tocopherols or tocotrienols. Further, vesicles were characterized by electron microscopy observations, transferrin assays, size distribution and zeta potential measurements. In vitro assessment was done by treating cancer cells in vitro to measure viability and cellular uptake of drug. In vivo experiments were carried out by i.v. administration of the vesicles into tumor bearing mice. Upon testing the in vivo efficacy, it was observed that α tocotrienol alone has significant efficacy against cancer cells in vivo. The tumor regression was observed starting day 1 until 11 days. Later, few tumors still maintained regression under influence of α tocotrienol treatment. However, all other tocotrienols were targeted to the site with transferrin conjugated vesicles. Moreover, there is no sign of any toxicity in the animals underwent treatment [44].

Conclusion

Other than the biological properties mentioned in this review, tocotrienols exert many other activities including bone resorption, diabetes, cardiovascular and neurological diseases in vitro and in vivo. A lot much research is needed further to make them use in drug market. Tocotrienols also prevents or provides protection against Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease. To avoid the problems with poor availability novel pro drug derivatives, semisynthetic derivatives, and delivery systems such as nano particles, nano emulsions, and sustained release formulations can be developed. Also we can take advantage of synergistic properties of tocotrienols with other available chemotherapeutic agents.

Conflict of Interest

Authors do not have any conflict of interest to declare.

References
